VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

148

Guidance for Industry

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing VICH GL32

DRAFT GUIDANCE

(For Comment Purposes Only)

This draft guidance consolidates developmental toxicity testing recommendations of the EU, Japan, and the USA for establishing the safety of veterinary drug residues in human food.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should be identified with the Docket No. 02D-0369.

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Center for Veterinary Medicine
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STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: DEVELOPMENTAL TOXICITY TESTING

Recommended for Consultation
at Step 4 of the VICH Process
on 11 April 2002
by the VICH Steering Committee

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing

TABLE OF CONTENTS

This draft guidance represents the agency's current thinking on developmental toxicity testing and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies the requirements of the applicable statutes and regulations.

1. Introduction

1.1. Objective of the guidance

A number of toxicological evaluations are recommended including the identification of any potential effects on prenatal development to establish the safety of veterinary drug residues in human food. The objective of this guidance is to recommend that developmental toxicity assessment is performed according to an internationally harmonized guidance. This guidance describes the test designed to provide information concerning the effects on the pregnant animal and on the developing organism following prenatal exposure.

1.2. Background

The assessment of the potential for developmental toxicity has been identified as one of the key areas to be considered in the evaluation of the safety of residues of veterinary drugs in human food. There has been considerable commonality in the methodology that has been used to test chemicals, human drugs, and veterinary drugs. This guidance consolidates developmental toxicity testing recommendations of the EU, Japan, and the USA for establishing the safety of veterinary drug residues in human food.

The approach to reproductive and developmental toxicity testing of veterinary drugs differs from that adopted by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[1]. The ICH guidance advocates a combination of three studies, in which dosing covers a number of stages that include premating to conception, conception to implantation, implantation to closure of hard palate, closure of the hard palate to the end of pregnancy, birth to weaning and weaning to sexual maturity. While such an approach is considered appropriate for most human drugs, exposure to veterinary drug residues in human food may be long-term, potentially throughout life. For this reason, this guidance, in conjunction with the Reproduction Testing Guidance (see VICH GL22), is believed to be more appropriate for assessing the safety of veterinary drug residues in human food. This guidance focuses on one stage of potential exposure, from implantation through the entire period of gestation to the day before caesarean section. This guidance provides harmonized guidance on the core recommendation for a developmental toxicity study for the safety evaluation of veterinary drug residues in human food.

The current guidance is one of a series of guidances developed to facilitate the mutual acceptance of safety data necessary for the determination of Acceptable Daily Intakes (ADI) for veterinary drug residues in human food by the relevant regulatory authorities. This guidance should be read in conjunction with the guidance on the general approach for the safety evaluation of veterinary drug residues in human food (VICH GL-33). It was developed after consideration of the existing ICH guidance for pharmaceuticals for human use on “Detection of Toxicity to Reproduction for Medicinal Products” [1], in conjunction with the current practices for evaluating veterinary drug residues in human food in the EU, Japan, USA, Australia and New Zealand.

1.3. Scope of the guidance

This document provides guidance for developmental toxicity testing for those veterinary medicinal products used in food-producing animals. However, it does not limit the studies that may be performed to establish the safety of residues in human food with respect to developmental toxicity. The guidance does not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why developmental toxicity data may not need to be provided.

1.4. General principles

The aim of developmental toxicity testing is to detect any adverse effects on the pregnant female and development of the embryo and fetus consequent to exposure of the female from implantation through the entire period of gestation to the day before caesarean section. Such adverse effects include enhanced toxicity relative to that observed in non-pregnant females, embryo-fetal death, altered fetal growth, and structural changes. Teratogenicity is defined as the capability of producing fetal malformation, i.e. a structural change considered detrimental to the animal, which may or may not be compatible with life.

The design of the test should be such that where any adverse effects on development are detected, the dose(s) at which they occur and the dose(s) producing no adverse effects are clearly identified. Some observations may suggest further study to fully characterize the nature of the response or of the dose-response relationship.

Traditionally, two species, one rodent and one non-rodent, have been used for developmental toxicity testing. Two species are still recommended under the ICH testing guidance for developmental toxicity testing for human drugs. However, a review of an extensive database for veterinary products indicated that a tiered approach would provide sufficient data to evaluate veterinary drugs for developmental toxicity while reducing the number of animals used in testing. This approach is described below.

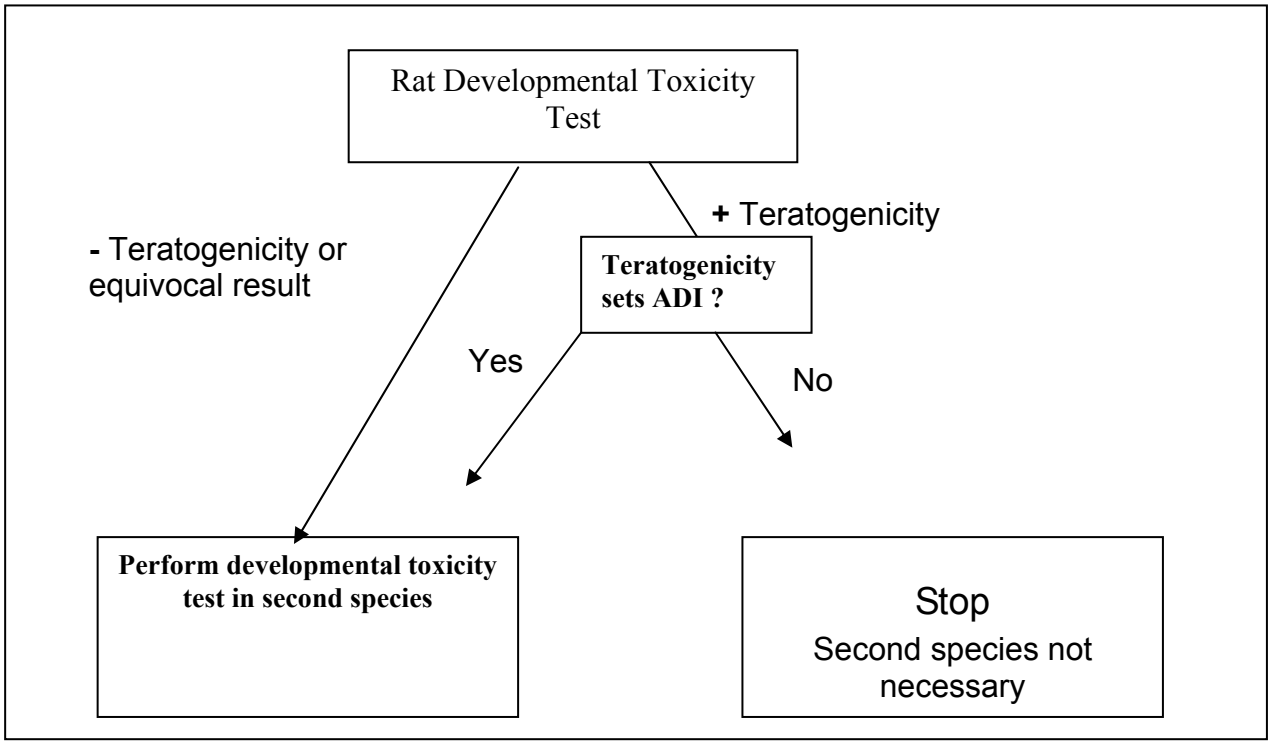
2. GUIDANCE

2.1. Number of species

The tiered approach (see Figure 1) begins with developmental toxicity testing in the rat. If clear evidence of teratogenicity is observed, regardless of maternal toxicity, testing in a second species would not be recommended, except under the circumstances described in the next paragraph. If a negative or an equivocal result for teratogenicity is observed in the rat, a developmental test in a second species, preferably the rabbit, should be conducted. In the absence of teratogenicity, a developmental toxicity test in a second species is recommended even if there are other signs of developmental toxicity (i.e. fetotoxicity or embryolethality).

If, upon review of all the core studies, it is apparent that the ADI would be based on teratogenicity occurring in the rat, a second developmental toxicity study should be conducted in another species. It is therefore recommended that a tiered approach beginning with a test in the rat be conducted. The outcome of this initial test should indicate whether a developmental test in a second species should be conducted.

Figure 1



2.2. Recommended test protocol

The OECD Test Guideline 414 "Prenatal Developmental Toxicity Study" [2] is an appropriate reference method for a developmental toxicity test to establish the human food safety of veterinary drugs used in food-producing animals. This test guidance includes discussion of the number of the test animals, administration period, selection of doses, observations of the dams, examination of the fetuses, and reporting of results.

3. REFERENCES

1. ICH. 1993. ICH Harmonised Tripartite Guideline S5A. Detection of Toxicity to Reproduction for Medicinal Products. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2. OECD. 2001. Test Guideline 414. Prenatal Developmental Toxicity Study. In: OECD Guidelines for the Testing of Chemicals. Organisation for Economic Cooperation & Development, Paris.